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Association of daily asthma emergency department visits and hospital admissions with ambient air pollutants among the pediatric Medicaid population in Detroit: Time-series and time-stratified case-crossover analyses with threshold effects

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ABSTRACT

Background: Asthma morbidity has been associated with ambient air pollutants in time-series and case-crossover studies. In such study designs, threshold effects of air pollutants on asthma outcomes have been relatively unexplored, which are of potential interest for exploring concentration–response relationships.

Methods: This study analyzes daily data on the asthma morbidity experienced by the pediatric Medicaid population (ages 2–18 years) of Detroit, Michigan and concentrations of pollutants fine particles ($PM_{2.5}$), CO, NO_2 and SO_2 for the 2004–2006 period, using both time-series and case-crossover designs. We use a simple, testable and readily implementable profile likelihood-based approach to estimate threshold parameters in both designs.

Results: Evidence of significant increases in daily acute asthma events was found for SO_2 and $PM_{2.5}$, and a significant threshold effect was estimated for $PM_{2.5}$ at 13 and 11 $\mu g\,m^{-3}$ using generalized additive models and conditional logistic regression models, respectively. Stronger effect sizes above the threshold were typically noted compared to standard linear relationship, e.g., in the time series analysis, an interquartile range increase (9.2 $\mu g\,m^{-3}$) in $PM_{2.5}$ (5-day-moving average) had a risk ratio of 1.030 (95% CI: 1.001, 1.061) in the generalized additive models, and 1.066 (95% CI: 1.031, 1.102) in the threshold generalized additive models. The corresponding estimates for the case-crossover design were 1.039 (95% CI: 1.013, 1.066) in the conditional logistic regression, and 1.054 (95% CI: 1.023, 1.086) in the threshold conditional logistic regression.

Conclusion: This study indicates that the associations of SO_2 and $PM_{2.5}$ concentrations with asthma emergency department visits and hospitalizations, as well as the estimated $PM_{2.5}$ threshold were fairly consistent across time-series and case-crossover analyses, and suggests that effect estimates based on linear models (without thresholds) may underestimate the true risk.

1. Introduction

Asthma causes a significant burden in children and is the principal reason for preventable pediatric hospitalizations. Studies since the mid-1980s, typically using daily counts of asthma events and Poisson regression models, have associated air pollutant exposures to acute asthma exacerbations, which are surrogate measures of asthma attacks (Andersen et al., 2007; Babin et al., 2007; Moura et al., 2009; Stieb et al., 2009). Such time-series data also have been examined using case-crossover analyses (Barnett et al., 2005; Jalaludin et al., 2008; Lin et al., 2003; Villeneuve et al., 2007), which are equivalent to Poisson regression models when the case ascertainment period and exposure status for the study cohort are the same at each time point (Lu and Zeger, 2007; Navidi, 2008). However, the stability and consistency of estimation of threshold parameters under both designs have not been studied. While several pilot studies examining mortality and morbidity endpoints and cardio-respiratory outcomes other than asthma have considered non-linear and specifically threshold-type concentration–response relationships

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(Brook, 2008; Daniels et al., 2000; Dominici et al., 2002; Kim et al., 2004; Pope and Dockery, 2006; Schwartz and Zanobetti, 2000; Schwartz et al., 2002), relatively few asthma studies have explored such models to study the relationship between pollutant exposures and acute childhood asthma events. Instead, previous studies investigating such associations have focused on linear relationships.

In this paper, we examine associations between daily air pollutant levels and asthma emergency department visits and hospital admissions for the pediatric Medicaid population in Detroit, Michigan. We explore potential threshold effects using Poisson regression under the framework of generalized additive models (Hastie and Tibshirani, 1986, 1990), and also under the time-stratified case-crossover design using conditional logistic regression models. Threshold effects have a distinct relevance in air pollution epidemiology: they have a plausible biological basis, and their results are easy to communicate and interpret since the regression coefficients show effects occurring above (and possibly below) a certain concentration. Our goals in this paper are to (1) determine whether daily changes in asthma emergency department visits and hospital admissions related to asthma among the pediatric Medicaid population in Detroit are attributable to fluctuations in ambient air pollutant concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), (2) evaluate whether asthma emergency department visits and hospital admissions show an exposure threshold, and compare the risks estimated by models with and without thresholds, and (3) examine whether estimated thresholds and the inferential results are consistent across the two analytical approaches, namely time-series and time-stratified case-crossover analyses. An auxiliary objective is to provide a simple and readily implementable method to estimate thresholds for GAMs and conditional logistic regression models that avoids use of complex non-linear optimization routines.

2. Materials and methods

2.1. Study population and health data

Medicaid beneficiary and claims data were obtained from the Michigan Data Warehouse of the Michigan Department of Community Health. These data provide the most complete and readily available source of healthcare utilization for the Detroit Medicaid-insured population. The population consists mainly of African–American children from lower income families (Wu and Batterman, 2006). African Americans are disproportionally affected by asthma and have greater morbidity compared to other races even after for controlling for socio-economic status, and thus are considered a high risk population for asthma-related events (Lieu et al., 2002). Beneficiary files were used to identify all children less than 18 years of age enrolled in Medicaid and residing in a Detroit zip code in the study period 2004–2006. To ensure a full-claims history, the study population was restricted to those with continuous Medicaid enrollment (not less than 11 months), full Medicaid coverage, and no other insurance. Extracted data included encrypted Medicaid identifier, age, sex, race/ethnicity, date and residence location as geocoded coordinates at the time of visit, and diagnostic codes. Claims for asthma emergency department visits and hospitalizations were identified as those with any mention of diagnostic code 493.X (International Classification of Diseases, 9th Revision, Clinical Modification). Claims were de-duplicated into unique encounters, and further restricted to exclude services at out-of-state locations. We excluded individuals with two consecutive claims within 30 days to ensure that the same exposure was not considered as case and control exposure when using time-stratified case-crossover analyses with calendar month as the reference frame. However, we did include individuals with multiple claims who did not fall under the above exclusion criterion. The resulting daily asthma claims were defined as daily counts of the sum of three mutually exclusive endpoints: emergency department visits without hospitalization, direct admits for hospitalization, and hospitalizations admitted through the emergency department. Daily asthma claims were further restricted to children 2–18 years of age (children between their second and eighteenth birthdays) due to the difficulty of accurately diagnosing asthma in very young children (0–2 years of age). Asthma claims were summarized in the form of counts and percentage counts across gender, race and age groups.

2.2. Air pollutant and meteorological measurements

Air quality data and meteorological data were obtained from the Michigan Department of Natural Resources and the Environment, and from Environment Canada. These included daily or hourly measurements of CO, NO_2, SO_2 and $PM_{2.5}$ monitored at four air quality monitoring sites in the Detroit metropolitan area (Allen Park, Dearborn, East 7 Mile and Linwood, Appendix A.1), 12 other sites in Michigan, and nine additional sites in Ontario, Canada. Surface meteorological data, including hourly measurements of temperature, relative humidity and barometric pressure, were obtained from the Detroit City Airport weather station.

Pollutants were included in the analysis if at least 20% of the observations exceeded the method detection limit and if at least 50% of the days had data available. Measurements less than or equal to the method detection limit were set to 1/2 of the limit. Daily averages for each pollutant at each site were computed from hourly data if at least 75% of the hourly data were available and considered valid. Another criteria pollutant, ozone (O_3), is monitored in the study region at two locations in Detroit, but unfortunately only during the warmer period. Because we noted significant differences between O_3 levels in Detroit and Windsor, Canada, and because over half of the study period did not have local O_3 data, we opted not to include this pollutant. We recognize the role of O_3 in respiratory effects; however, its omission does not invalidate the results obtained for the other pollutants as it is not identified as a potential confounder based on a correlation analysis of O_3 with the other pollutants.

The average pollutant level in Detroit was computed as the average concentration among the four Detroit monitoring sites, when available. CO was averaged from Allen Park and Linwood; NO_2 and SO_2 were averaged from East 7 Mile and Linwood. Daily $PM_{2.5}$ data were unavailable for 199 days at Allen Park and were collected only every 3rd day at the other three Detroit sites (Dearborn, East 7 Mile, Linwood). These four sites sampled and weighed $PM_{2.5}$ on filters following the Federal Reference Method, and observations at these sites were highly correlated ($\rho = 0.92 - 0.95$) and had similar distributions. Hourly $PM_{2.5}$ concentrations were measured at two sites in the city of Windsor, Canada, immediately across the Detroit River from Detroit, using tapered element oscillating microbalances. We used the tapered element oscillating microbalances data to impute daily Federal Reference Method $PM_{2.5}$ concentrations at Allen Park. Because daily Federal Reference Method and tapered element oscillating microbalances concentrations were highly correlated ($\rho = 0.90$), we fitted a linear mixed model with a first-order auto-regressive error term to estimate Federal Reference Method $PM_{2.5}$:

$$PM_{AP} = \beta_0 + \beta_1\ PM_{Win} + \beta_2\,\text{Season} + \beta_3\,\text{Temp} + \beta_4\,\text{RH} + \beta_5 P + \beta_6\,PM_{Win}\,\text{Temp} + \varepsilon \quad (1)$$

where PM_{AP} is the daily $PM_{2.5}$ concentration in Allen Park ($\mu g\,m^{-3}$), PM_{Win} is the daily averaged $PM_{2.5}$ concentration in downtown Windsor ($\mu g\,m^{-3}$), season is the factor effect of seasons (spring=March–May, summer=June–August, fall=September–November, winter=December–February), Temp is the daily average temperature (°C), RH is the daily average relative humidity (%), and P is the daily average atmospheric pressure (Pa). Apart from the main effects, model (1) includes an interaction term between $PM_{2.5}$ and temperature. The autocorrelation structure on the measurement error term implies that correlation between successive $PM_{2.5}$ concentrations depends on the time lag of measurements, namely, the measurement on the ith and jth day depend only on the difference $|i-j|$ with $\text{corr}(\varepsilon_i, \varepsilon_j) = \rho^{|i-j|}$. Parameters β_0–β_6 were first estimated using 700 randomly selected days from the 897 available at Allen Park over the 3-year study period (a total of 1096 days). The remaining 197 days were used as a validation data set. Prediction accuracy was assessed using the correlation between observed and predicted $PM_{2.5}$ concentrations, and the distribution of differences between observed and predicted values in the validation data set. A complete time-series record of daily $PM_{2.5}$ concentrations in Allen Park was derived this way and used as a measure of $PM_{2.5}$ exposure.

Descriptive analyses of each pollutant were carried out to show distributional patterns, correlations, outliers and missing data, and to identify weekly, seasonal and long-term trends.

2.3. Time-series models

We fitted generalized additive models by aggregating data across the 3 years (2004–2006). Single pollutant Poisson regression models with a log-linear link were fitted using the daily counts of asthma events as the outcome. These models included meteorological variables (Temp and RH, variables as defined in Eq. (1)), day of week, and seasonal trends that were identified as potential covariates by either bivariate analysis with the health outcomes or in the literature. We separately tested pollutant exposures using 1 through 5-day lags, as well as 2-, 3- and 5-day moving averages. To account for other temporal trends, nonparametric terms were used for time and Temp. The single-pollutant generalized additive model was of the form

$$\log E(Y) = \beta_0 + \beta_1\,\text{Con} + \beta_2\,\text{Season} + \beta_3\,\text{DOW} + \beta_4\,\text{RH} + \text{Spline(Temp)} + \text{Spline(Time)} \quad (2)$$

where Y is the daily counts of asthma events, Con is the air pollutant concentration, DOW is the day of week, Spline(Time) or Spine(Temp) is the penalized regression spline term with time or temperature as its argument. The smoothing parameters were estimated using generalized cross-validation methods as implemented in the MGCV package in R (Wood, 2006; R Development Core Team, 2010). In all analyses, we also explored the possibility of including a spline term corresponding to RH and noted that it was always determined to be statistically indistinguishable from a linear term. Thus we simplified the models to only include linear term for RH. There was no evidence of instability in estimation due to modest correlation between the meteorological variables in model (2). To visualize concentration–response curves relating daily asthma counts and pollutant exposures, we examined a similar generalized additive model that used a third smoothing term on the air pollutant concentration. The estimated spline terms for concentration were used to display the pattern of a possible non-linear concentration–response relationship. However, numerical results from this model are not discussed here. Rather, our focus is a particular sub-class of non-linear models, specifically change-point models, which allow for possible threshold effects. Namely, to investigate threshold effects, we considered the following generalized additive model:

$$\log E(Y) = \beta_0 + \beta_1\,\mathrm{Con} + \beta_2(\mathrm{Con}-\xi)_+ + \beta_3\,\mathrm{Season} + \beta_4\,\mathrm{DOW} + \beta_5\,\mathrm{RH} + \mathrm{Spline(Temp)} + \mathrm{Spline(Time)} \quad (3)$$

where function $(\mathrm{Con}-\xi)_+ = \max\{\mathrm{Con}-\xi,\ 0\}$. This model is equivalent to the following:

$$\log E(Y) = \begin{cases} \beta_0 + \beta_1\,\mathrm{Con} + \text{other covariates} & \text{if Con} < \xi \\ \beta_0 - \beta_2\xi + (\beta_1+\beta_2)\mathrm{Con} + \text{other covariates} & \text{if Con} \geq \xi \end{cases}$$

where the two regression equations meet at $\mathrm{Con}=\xi$. The more familiar form of a threshold model assumes $\beta_1=0$ in the model specification, i.e., there is no effect of the exposure below the threshold. However, this assumption needs to be carefully used and to be based on formal test that $H_0 : \beta_1 = 0$ in Eq. (3). We do consider this special sub-class of models as a part of our sensitivity analysis, but the more general model (3) remains the primary model we consider.

The two regression segments corresponding to the concentration meet at threshold ξ, thus avoiding discontinuities in the concentration–response relationship. A test for differences in effects above and below the threshold, i.e., no significant threshold effect, is obtained by testing $H_0 : \beta_2 = 0$, where $\hat{\boldsymbol{\beta}}$ is the maximum likelihood estimate of the regression parameters in Eq. (3) for a given ξ (Kim et al., 2004). For a fixed value of ξ, the profile penalized log-likelihood requires fitting a single generalized additive model with linear terms in the two exposure components, followed by optimizing the likelihoods for varying ξ over a given range. We considered ξ ranging from the 10th to 95th percentile concentrations of the exposure in our grid search. Threshold ξ estimated in this manner closely approximates its maximum likelihood estimate. In all of the time-series models we allowed for overdispersion relative to the Poisson variance, and used Dean's test to formally test for overdispersion (Dean, 1992).

2.4. Case-crossover designs

Case-crossover designs (Maclure, 1991) have been widely used to study the effect of short-term air pollution exposure and the risk of acute adverse health event. Under this design, for each case, exposure at the index time is compared to exposure of the same case at a referent time. The design inherently controls for effects of time-invariant subject-specific covariates (e.g., age, gender and race), potential time-varying confounders (e.g., day of week and seasonal and secular trends) with appropriate choice of the referent time windows. Additionally, by use of self-controls, the design controls for individual-level confounders, e.g., the severity of the underlying disease, self-management behavior, and personal asthma episode triggers. Thus, the time-series analysis models the effect of confounders, whereas a case-crossover design controls them by design. The time-stratified selection strategy is more generally valid than any of the alternatives thus far proposed (Janes et al., 2005a; Mittleman, 2005). Lumley and Levy (2000) and Janes et al. (2005b) present additional discussion of the overlap bias that may occur in case-crossover studies.

We chose time-stratified referent selection with strata chosen as the calendar month and matched by day of week. Exposures on the same day of the week during the same calendar month as the case-event serve as control exposures. Under this sampling strategy, conditional logistic regression models adjusted for meteorological variables of Spline(Temp) and RH were used. Moreover, to fit conditional logistic regression models with thresholds, we again adopted a conditional profile likelihood technique similar to that proposed for generalized additive models, i.e., the usual conditional logistic regression models were fitted with the two exposure variables Con and $(\mathrm{Con}-\xi)_+$ (see details in Appendix A.2). We again carried out a grid search for the location of the threshold value ξ that maximized the conditional profile likelihood $l_c(\xi,\hat{\boldsymbol{\beta}})$. All conditional logistic regression models were assessed for potential outliers and influential observations, using the model diagnostics proposed by Lu et al. (2008).

Fitted regressions for the generalized additive models and conditional logistic regression models were summarized using risk and odds ratios with 95% confidence intervals, respectively. Model comparison was carried out by examining the Akaike information criterion. The significance ($P<0.05$) of the threshold effect was evaluated using the Wald χ^2 test for the regression coefficient corresponding to $(\mathrm{Con}-\xi)_+$.

3. Results

3.1. Summary of exposure measures and asthma events

Table 1 summarizes the air quality and meteorological data in Detroit from 2004 to 2006. Over the 3-year period, the mean daily air pollutant levels were 0.42 ppm for CO, 16.8 ppb for NO_2, 3.77 ppb for SO_2, and 15.0 $\mu g\,m^{-3}$ for $PM_{2.5}$. (Annual summaries are reported in Appendix A.3.) Table 2 shows Spearman correlations between pollutants at the various Detroit monitoring sites. A scatterplot of the observed versus predicted $PM_{2.5}$ values and a histogram of prediction errors for the 197 validation days is shown in Appendix A.4. The imputed data accurately matched most of the observations with a correlation $\rho=0.93$, and errors were generally well below 3 $\mu g\,m^{-3}$.

Descriptive analyses of asthma events by age group, gender, race and season are shown in Table 3. A total of 12,933 asthma events in the 2–18 year age group were observed for 7063 children during the 1096 days of the 2004–2006 period, representing an average rate of 11.8 events/day. Our composite endpoint of acute asthma events included three types of claims. Of the total number of claims, 80.3% were for emergency department visits without hospitalizations, 11.9% were for emergency department visits that ultimately led to hospitalizations, and 7.8% were for direct admit to hospitalizations. Of the 7063 children, 60.4% had 1 claim, 17.8% had 2 claims, 10.7% had 3 claims and the remainder had 4 or more claims. The long-term and smoothed trend of daily asthma events (Fig. 1) shows a strong seasonal pattern, with highest frequency during fall, and the lowest during summer.

Table 1
Summary of air pollutant exposure and meteorological variables in Detroit, Michigan, based on 24-h averages over 2004–2006.

Variables	Mean (SD[a])	Percentile					IQR[a]
		Min[a]	25%	Median	75%	Max[a]	
CO (ppm)[b]	0.42 (0.35)	0.05	0.21	0.35	0.52	3.05	0.31
NO_2 (ppb)	16.75 (7.28)	2.15	11.54	15.74	21.19	55.22	9.65
$PM_{2.5}$ ($\mu g\,m^{-3}$)	14.97 (7.93)	2.63	9.36	13.35	18.52	68.99	9.16
SO_2 (ppb)	3.77 (3.76)	0.50	1.09	2.45	5.11	27.25	4.02
Temperature (°C)	10.57 (10.32)	−13.66	2.05	11.04	19.77	31.00	17.72
Relative humidity (%)	69.98 (11.70)	31.04	61.54	70.04	78.42	98.96	16.88
Pressure (Pa)	1016.85 (7.27)	992.25	1012.48	1016.71	1021.21	1042.25	8.73

[a] IQR: interquartile range; Min: minimum; Max: maximum; SD: standard deviation.
[b] CO: daily 3-h average from 6 to 9 a.m.

Table 2
Spearman correlations for the daily 24-h pollutant concentrations in Detroit, Michigan, 2004–2006.

Pollutant and monitoring sites		CO[b]		$PM_{2.5}$ (FRM[a])				NO_2		SO_2	
		Allen Park	Linwood	Allen Park	Dearborn	East 7Mile	Linwood	East 7Mile	Linwood	East 7Mile	Linwood
CO	Allen Park	1.00									
	Linwood	0.68	1.00								
$PM_{2.5}$ (FRM)	Allen Park	0.30	0.39	1.00							
	Dearborn	0.26	0.41	0.93	1.00						
	East7Mile	0.31	0.38	0.94	0.92	1.00					
	Linwood	0.34	0.41	0.95	0.92	0.92	1.00				
NO_2	East7Mile	0.37	0.53	0.56	0.61	0.59	0.58	1.00			
	Linwood	0.40	0.56	0.61	0.66	0.66	0.64	0.87	1.00		
SO_2	East7Mile	0.21	0.31	0.50	0.51	0.53	0.52	0.49	0.55	1.00	
	Linwood	0.17	0.28	0.40	0.43	0.45	0.43	0.42	0.54	0.79	1.00

[a] FRM: federal reference method.
[b] CO: daily 3-h average from 6 to 9 a.m.

Table 3
Characteristics of study participants (children 2–18 years of age, continuously enrolled in Medicaid with full coverage and no other insurance). Data retrieved based on claims recorded for the pediatric Medicaid Population in Detroit, Michigan, 2004–2006.

Characteristics		Number of asthma patients	%	No. of asthma events	%
Gender	Female	2863	40.53	5119	39.58
	Male	4200	59.47	7814	60.42
Race	African–American	6498	92.00	12157	94.00
	Caucasian	237	3.36	377	2.92
	Hispanic	222	3.14	355	2.74
	Other	106	1.50	44	0.34
Age (years)	$2 \le \text{Age} < 5$	3090	34.65	5327	32.81
	$5 \le \text{Age} < 10$	1968	22.07	3945	24.29
	$11 \le \text{Age} < 18$	2005	22.49	3661	22.55
Season[a]	Spring			3211	24.83
	Summer			1866	14.43
	Fall			4732	36.59
	Winter			3124	24.16
Type of event	ED visits without hospitalization			10,386	80.31
	Direct admit to hospitalization			1014	7.84
	Hospitalizations admitted through the ED			1533	11.85
Total		7063	100	12,933	100

[a] Season: spring=March–May, summer=June–August, fall=September–November, winter=December–February.

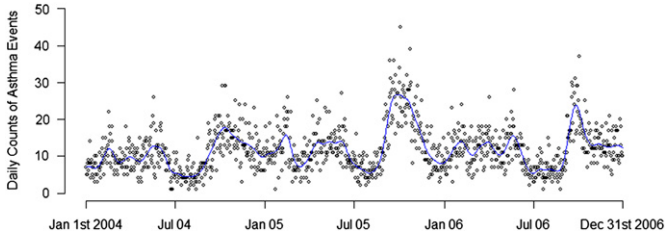

Fig. 1. Trend of daily counts of asthma events for the pediatric Medicaid population (children 2–18 years of age) in Detroit, Michigan, 2004–2006. Daily observations are shown as points with locally estimated scatter-plot smoothing trend shown as overlaying fitted curve. The endpoints of asthma events include emergency department visits without hospitalization, direct admission for hospitalization, and hospitalizations admitted through the emergency department.

3.2. Association of asthma claims with air pollutants

Table 4 shows results of the time-series generalized additive models and case-crossover conditional logistic regression models (both without thresholds) for the four pollutants and selected lags for the 3-year study period. (Results for all lags and moving averages are shown in Appendices A.5 and A.6.) Estimated measures of association, including risk ratios, odds ratios and 95% confidence intervals for daily asthma visits, are shown for an interquartile range increase in pollutant concentrations. Both generalized additive model and conditional logistic regression models show strong evidence of significant increases in daily asthma events with increasing SO_2 concentrations for 3, 4 and 5-day lags, and for 3- and 5-day moving averages. Evidence of associations to 2-day lag or 2-day moving average was also found using conditional logistic regression. For example, the estimated risk ratios for daily asthma events associated with an interquartile range increase (4.02 ppb) in SO_2 concentration was 1.031 (95% CI: 1.008, 1.055) for the generalized additive model, and the estimated odds ratio was 1.031 (95% CI: 1.010, 1.052) for the conditional logistic regression models, using a 3-day lag. Strong evidence of associations between daily asthma events with $PM_{2.5}$ concentrations for 3, 4 and 5-day lags, as well as for 5-day moving averages were found using both generalized additive models and conditional logistic regression models. CO and NO_2 were significant only for the 4- or 5-day lags. The effect sizes as well as their 95% CIs are consistent across the two models considered for each pollutant. We did not find evidence of a significant association for a 1-day lag for any pollutant. The overdispersion parameter

Table 4
Comparison of GAMs[a] and time-stratified case-crossover CLRs[a] without thresholds; estimated risk and odds ratios for daily asthma events and an one interquartile range increase of a pollutant exposure for the pediatric (children 2–18 years of age) Medicaid population in Detroit, MI, 2004–2006.

	GAM without threshold				**Case-crossover CLR without threshold**			
	RR[a]	95% CI[a]		QAIC[a]	OR[a]	95% CI		AIC[a]
NO_2 (ppb)								
3-Day lag	1.013	0.981	1.047	6225	1.013	0.984	1.043	100,751[b]
5-Day lag	**1.038**	**1.005**	**1.072**	6202[b]	**1.039**	**1.010**	**1.070**	101,195
3-Day moving average[a]	0.972	0.930	1.016	6317	1.006	0.968	1.046	103,616
5-Day moving average	1.014	0.961	1.070	6333	1.043	0.996	1.093	104,039
SO_2 (ppb)								
3-Day lag	**1.031**	**1.008**	**1.055**	6198	**1.031**	**1.010**	**1.052**	101,061[b]
5-Day lag	**1.040**	**1.017**	**1.064**	6191[b]	**1.042**	**1.021**	**1.064**	101,666
3-Day moving average	**1.037**	**1.003**	**1.073**	6322	**1.049**	**1.019**	**1.081**	103,873
5-Day moving average	**1.078**	**1.035**	**1.122**	6315	**1.086**	**1.049**	**1.124**	104,021
CO (ppm)								
3-Day lag	0.991	0.972	1.011	6324	1.002	0.984	1.020	103,928
5-Day lag	**1.023**	**1.004**	**1.043**	6308[b]	**1.021**	**1.003**	**1.039**	103,829[b]
3-Day moving average	0.970	0.941	1.000	6328	0.996	0.970	1.023	104,042
5-Day moving average	1.003	0.967	1.041	6334	1.022	0.989	1.056	104,040
$PM_{2.5}$ ($\mu g\, m^{-3}$)								
3-Day lag	**1.029**	**1.006**	**1.052**	6323	**1.032**	**1.011**	**1.052**	103,921
5-Day lag	**1.036**	**1.014**	**1.059**	6311[b]	**1.036**	**1.016**	**1.056**	103,825[b]
3-Day moving average	1.012	0.985	1.040	6334	1.018	0.994	1.042	104,040
5-Day moving average	**1.030**	**1.001**	**1.061**	6332	**1.039**	**1.013**	**1.066**	104,036

Bold: The RRs or ORs are statistically significant (P-value <0.05).

[a] AIC: Akaike information criterion; QAIC: quasi-Akaike information criterion; CI: confidence interval; CLR: conditional logistic regression; GAM: generalized additive model; RR: risk ratio; OR: odds ratio; moving average: average for the specified number of days preceding the asthma events.

[b] The QAIC or AIC is the smallest among all lags for each pollutant.

significantly differed from unity in most of the fitted generalized additive model models using Dean's test, thus we considered overdispersion in all models.

Fig. 2 shows the logarithm of the profile likelihoods for threshold ξ in both time-series generalized additive models and case-crossover conditional logistic regression models, using the lagged 5-day moving average of pollutant. The same, or nearly the same, threshold was identified in both generalized additive models and conditional logistic regression models for each pollutant. We performed parallel analyses for other exposure lags and moving averages, and found that threshold locations were consistent with respect to lag specification. Thus, a single threshold value was used across all lags and moving averages. An alternative is to search for a separate ξ for each lag, season or year, which complicates comparability and interpretability of effect estimates. Table 5 shows results including risk ratios and odds ratios for effects above the threshold, the 95% confidence intervals, and the significance of the threshold effect based on the Wald test for H_0: $\beta_2=0$, i.e., the regression coefficient corresponding to $(\mathrm{Con}-\xi)_+$. These results suggest no evidence of threshold effects for CO, NO_2 or SO_2 with respect to asthma outcomes. In contrast, significant threshold effects in both generalized additive models and conditional logistic regression models were detected for $PM_{2.5}$ with an estimated threshold of 13 and 11 $\mu g\, m^{-3}$, respectively. Effects above the $PM_{2.5}$ threshold, as seen in Table 5, were somewhat diluted in Table 4 since effects both below and above the threshold were captured by a single parameter. For example, the estimated risk ratio for daily asthma visits associated with an interquartile range increase (9.2 $\mu g\, m^{-3}$) of $PM_{2.5}$ (at 5-day moving averages) had a risk ratio of 1.030 (95% CI: 1.001, 1.061) in the linear generalized additive model, and 1.066 (95% CI: 1.031, 1.102) in the threshold generalized additive model. The corresponding estimates under case-crossover design were 1.039 (95% CI: 1.013, 1.066) in the linear conditional logistic regression model, and 1.054 (95% CI: 1.023, 1.086) in the threshold conditional logistic regression model. Thus, the ability to simply search and test for the significance of a threshold effect was informative for both time-series and case-crossover approaches. We also noted that treating pollutant effects via a nonparametric spline term in generalized additive model or conditional logistic regression could provide insight into the concentration–response relationship. Fig. 3 presents the estimated spline terms of pollutants, and one can distinctly notice non-linear patterns for some pollutants, especially $PM_{2.5}$.

Testing results of $H_0: \beta_1=0$, i.e., the regression coefficient corresponding to concentration below the threshold level ξ, show no significant evidence. To compare our results with a more common version of the threshold model which assume $\beta_1=0$, we fitted the $PM_{2.5}$ models under this additional constraint. Appendix A.7 presents results indicating that inferential results remained unchanged for effects of $PM_{2.5}$ concentrations above the threshold, although there are minor numerical differences in parameter estimates.

We assessed the presence of outliers and influential observations for each model using diagnosis proposed by Lu et al. (2008). For example, Fig. 4 presents a normal quantile–quantile plot of standardized residuals and DFFITS statistics (the change in the predicted value for a point, obtained when that point is left out of the regression) for each day before and after removing outliers, using 5-day moving average of $PM_{2.5}$. The standardized residuals under the Poisson assumption should approximate a standard Gaussian distribution if the model is correctly specified. Thus the sample quantiles of the residuals should closely follow the normal quantiles under correct model specification, and the points on the quantile plot should lie about the equiangular $Y=X$ line. A total of 11 days had $|\text{sample quantiles}|>3.5$ in the generalized additive model; 6 days had $|\text{DFFITS}|>1.5$ in the conditional logistic regression model. Inferential results and coefficients obtained in analyses that omitted these outliers were largely unchanged, indicating that results presented with all data points are reasonably robust. Since different pollutant models gave rise to different sets of outlying and influential days, we performed this diagnostic process as a cautionary check with and without the suspect days

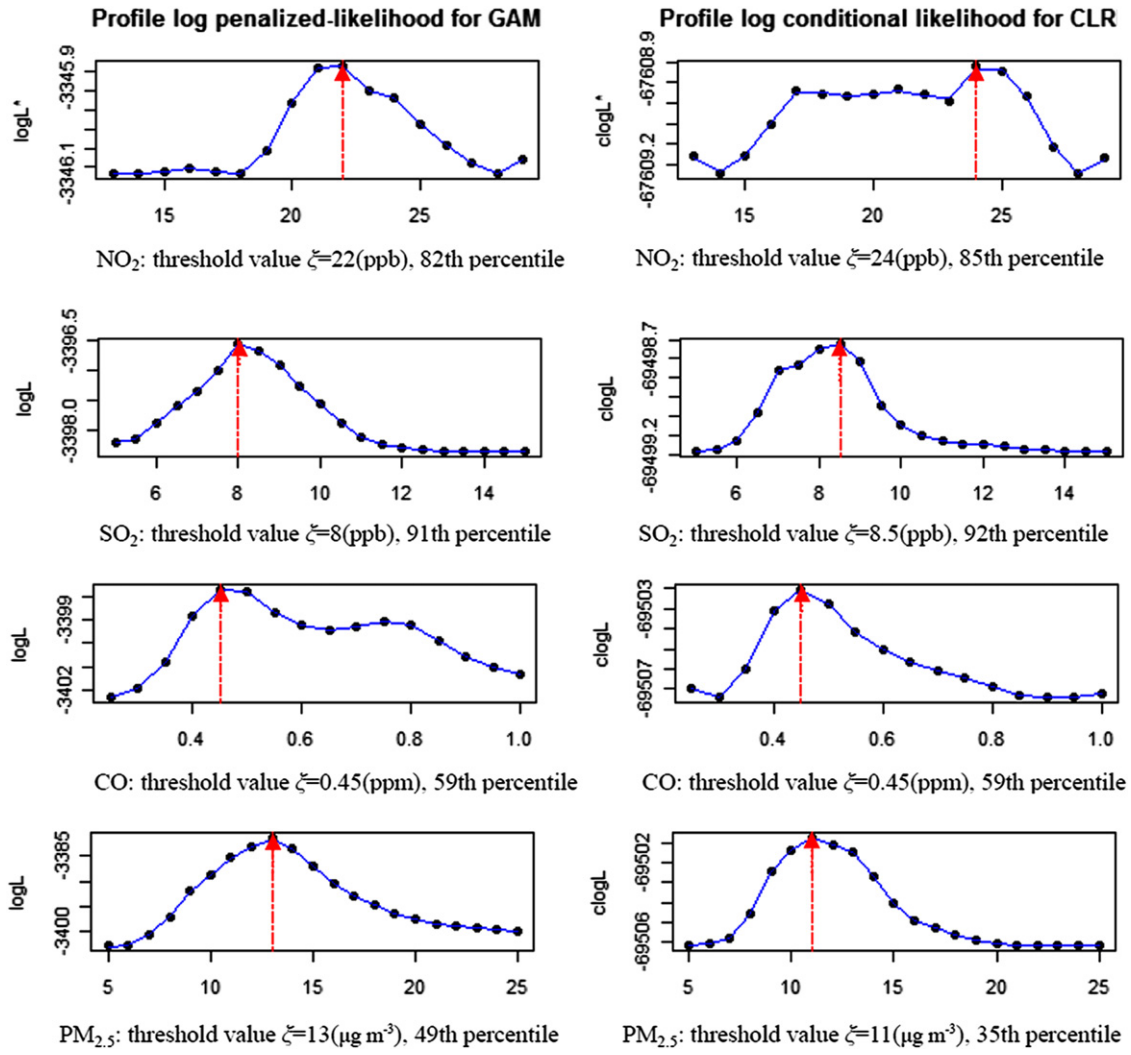

Fig. 2. Plots of logarithm of profile penalized-likelihood (*log *L*) of generalized additive model (GAM) and logarithm of profile conditional likelihood (*c log *L*) of conditional logistic regression (CLR), searching for the threshold parameters corresponding to each pollutant using 5-day moving average of pollutant concentration.

to ensure consistency of our results. The results shown in Tables 4 and 5 are based on all days for uniformity and comparability across models.

4. Discussion

Hospital admission and emergency department visits for asthma have been associated with air pollutants in both single and multiple city studies and using both time-series and case-crossover designs. Among the more recent literature, an Alaskan study of 1641 daily Medicaid claims for children using generalized estimating equations associated a 10 $\mu g\,m^{-3}$ increase in daily PM_{10} with a 0.6% (95% CI: 0.1, 1.3) increase in outpatient asthma visits and a 1.8% (95% CI: 0.6, 3.0) increase in inhaled quick-relief mediation prescriptions. Stronger results were found for weekly events and for upper quartile exposures (Chimonas and Gessner, 2007). This study used only one air monitor sited by a busy road, which may have resulted in exposure misclassification. Ten air monitoring sites were used in a study in Oklahoma City, USA, which used a negative binomial model to assess associations between air pollutant exposures based on the monitoring site closest to the child's residential zip code, and daily asthma hospital admissions for children 0–14 years old (Magas et al., 2007). NO_2 was a significant predictor with an additional 6.21 (95% CI: 0.68, 11.7) asthma hospitalizations per day for a 1 ppb increase; O_3 and $PM_{2.5}$ were not significant predictors. Daily asthma-related pediatric emergency department visits and hospital admissions in the District of Columbia, USA were associated with daily 8-h O_3 and 24-h $PM_{2.5}$ levels from three monitors using adjusted Poisson models (Babin et al., 2007). A 10 ppb O_3 increase was associated with a 4.5% (95% CI: 0.6, 8.5) increase in emergency department admissions for 1–17 year-old children; a larger effect (8.3%; 95% CI: 2.6, 14.4) was seen for 5–12 year-olds. Age was a significant effect modifier for asthma hospitalizations in a New York City study. Children age 6–18 years consistently had the highest risk, using daily time-series analysis (Silverman and Ito, 2010). In Copenhagen, marginally significant associations were found between PM_{10}, CO and NO_2 levels and asthma hospital admissions (Andersen et al., 2007). In Rio de Janeiro, semi-parametric Poisson regressions were used to explore associations between PM_{10}, SO_2, CO, NO_2 and O_3 and emergency department visits for bronchial obstruction in children aged 1–12 years (Moura et al., 2009). A significant increase of 6.7% (95% CI: 1.8, 11.5) in visits was associated with a 10 $\mu g\,m^{-3}$ PM_{10} increase for children 0–2 years. Evidence of the adverse effect of PM_{10} on pediatric asthma exacerbations and hospital admissions was also found in Athens, Greece, especially in 0–4 year olds (Nastos et al., 2010). In Tokyo, auto-regressive integrated moving average models were used to link emergency department asthma visits to

Table 5
Comparison of GAMs[a] and time-stratified case-crossover CLRs[a] with thresholds; estimated risk and odds ratios above the threshold for daily asthma events and an one interquartile range increase of a pollutant exposure for the pediatric (children 2–18 years of age) Medicaid population in Detroit, MI, 2004–2006. Otherwise as Table 4.

	GAM with threshold				Case-crossover CLR with threshold			
	RR[a]	95% CI[a]		QAIC[a]	OR[a]	95% CI		AIC[a]
NO_2 (ppb) ξ=23								
3-Day lag	0.957	0.882	1.039	6222.9	0.960	0.894	1.030	100,751.5[b]
5-Day lag	1.015	0.939	1.097	6203.1[b]	1.003	0.936	1.075	101,197.3
3-Day moving average[a]	0.937	0.845	1.039	6317.9	0.945	0.867	1.031	103,616.2
5-Day moving average	0.984	0.876	1.106	6334.9	0.958	0.867	1.059	104,038.4
SO_2 (ppb) ξ=8.25								
3-Day lag	1.036	0.983	1.093	6199.6	1.022	0.974	1.074	101,064.3[b]
5-Day lag	1.049	0.994	1.106	6192.4[b]	**1.057**	**1.006**	**1.110**	101,668.5
3-Day moving average	0.948	0.861	1.043	6317.4	0.917	0.842	0.998	103,865.1
5-Day moving average	1.026	0.900	1.170	6315.8	0.960	0.855	1.078	104,019.5
CO (ppm) ξ=0.45								
3-Day lag	0.998	0.972	1.025	6325.2	1.003	0.979	1.026	103,930.8
5-Day lag	1.008	0.982	1.034	6305.0[b]	1.009	0.986	1.033	103,829.5[b]
3-Day moving average	0.956	0.917	0.997	6328.3	0.966	0.932	1.002	104,038.4
5-Day moving average	0.968	0.920	1.018	6328.4	0.975	0.933	1.017	104,032.4
$PM_{2.5}$ ($\mu g\,m^{-3}$) ξ=12								
3-Day lag[c]	**1.046**	**1.017**	**1.075**	6320.4	**1.030**	**1.005**	**1.056**	103,921.0
5-Day lag[c]	**1.055**	**1.026**	**1.084**	6308.4[b]	**1.041**	**1.015**	**1.066**	103,824.9[b]
3-Day moving average	1.024	0.992	1.057	6334.3	1.007	0.980	1.036	104,038.8
5-Day moving average[c]	**1.066**	**1.031**	**1.102**	6317.9	**1.054**	**1.023**	**1.086**	104,033.1

Bold: the RRs or ORs above the threshold are statistically significant (P-value <0.05).
Underline: the QAIC/AIC of the threshold model is smaller than the QAIC/AIC from the corresponding linear model.

[a] AIC: Akaike information criterion; QAIC: quasi-Akaike information criterion; CI: confidence interval; CLR: conditional logistic regression; GAM: generalized additive model; RR: risk ratio; OR: odds ratio; Moving average: average for the specified number of days preceding the asthma events.

[b] The QAIC or AIC is the smallest among all lags for each pollutant.

[c] Significant threshold effect in GAMs with threshold and case-crossover CLRs with threshold, based on the Wald test for H_0:$\beta_2=0$, which is the regression coefficient corresponding to$(Con-\xi)_+$.

daily SO_2, NO, NO_x, suspended PM, CO, pressure and humidity measurements (Abe et al., 2009). Associations with pollutants were not statistically significant in the multi-pollutant model. In a case-crossover design, large increases in emergency department visits for asthma in young children (2–4 years of age) in Edmonton, Canada were associated with 5-day lagged concentrations of NO_2 and CO measured at three sites between April and September; smaller increases were also associated with O_3, PM_{10} and $PM_{2.5}$ (Villeneuve et al., 2007). Results of this 10 year study were largely unchanged after adjustments for aeroallergens. Another Canadian study, conducted in Toronto, found similar effects for NO_2 and CO in a case-crossover analysis examining children ages 6–12 (Lin et al., 2003). A recent case-crossover analysis examining emergency department visits in Sydney, Australia found the strongest associations for CO and children in the 5–9 and 10–14 years age groups; emergency department visits for younger children were associated with all pollutants investigated (CO, NO_2, O_3, $PM_{2.5}$ and PM_{10}) (Jalaludin et al., 2008).

Several multiple city studies have been conducted. A panel study of children in seven US and one Canadian cities and five criteria pollutants associated 2-day lagged CO and NO_2 concentrations with asthma exacerbation as measured by symptoms and rescue inhaler use (Schildcrout et al., 2006). Significant increase in respiratory-related emergency department visits across 14 hospitals in seven Canadian cities was associated with daily O_3, PM_{10} and $PM_{2.5}$ levels (2-day lag) using generalized linear models, especially in the warm season (Stieb et al., 2009). Another multiple city study, conducted in the five largest cities in Australia and the two largest in New Zealand, used case-crossover designs with respiratory hospital admissions for children 0–14 years, and a random effects meta-analysis to combine results across cities (Barnett et al., 2005). The only significant finding for asthma was a 6% (95% CI: 2.0, 12.1) increase for 5–14 year olds for an interquartile range (5.1 ppb) increase of NO_2. Effects were stronger in the warmer months, and no significant effects were seen in multiple pollutant models. In two Idaho, USA cities, daily PM_{10}, NO_2 and SO_2 were examined using generalized linear models and splines to relate hospital admissions and medical visits for respiratory disease (Ulirsch et al., 2007). A 24.3 $\mu g\,m^{-3}$ increase in PM_{10} was associated with 4.3% (P=0.06) increase in the total number of daily admissions for children 0–17 years of age.

Many of these studies have included children less than 2 years of age (Barnett et al., 2005; Magas et al., 2007; Moura et al., 2009; Nastos et al., 2010; Ulirsch et al., 2007). However, it is difficult to diagnose asthma in this age group until persistence of symptoms can lead to an asthma diagnosis. The misclassification of diagnoses of asthma in children less than 2 years of age might have resulted in invalid inference, especially for study populations that consist mainly of this age group, for example, Moura et al. (2009) and Nastos et al. (2010). It is also seen that some of these studies that found no evidence or marginal significant evidence of association might be probably due to the diagnosis misclassification issue, for example, Ulirsch et al. (2007). Therefore, children aged 0–2 years were excluded from our main analysis due to the possibility of differential diagnosis accuracy for asthma in this age group. A sensitivity analysis of 0–18 year olds revealed that effect sizes are indeed attenuated compared to the 2–18 years age group. Silverman and Ito (2010) have found that the peak pollution effects on asthma are observed in children of age approximately 7–12 years. An analysis stratified by age, e.g., ages 2–6, 7–12 and 13–18 years, could potentially provide more insight into the relative vulnerability of age groups in terms of exposure to pollutants. However, given the limited number of claims in each group (2–6 years: 6232; 7–12 years: 4292; 13–18 years: 2409; with an average rate of 5.7, 3.9, 2.2 event/day, respectively), we refrain from presenting this analysis.

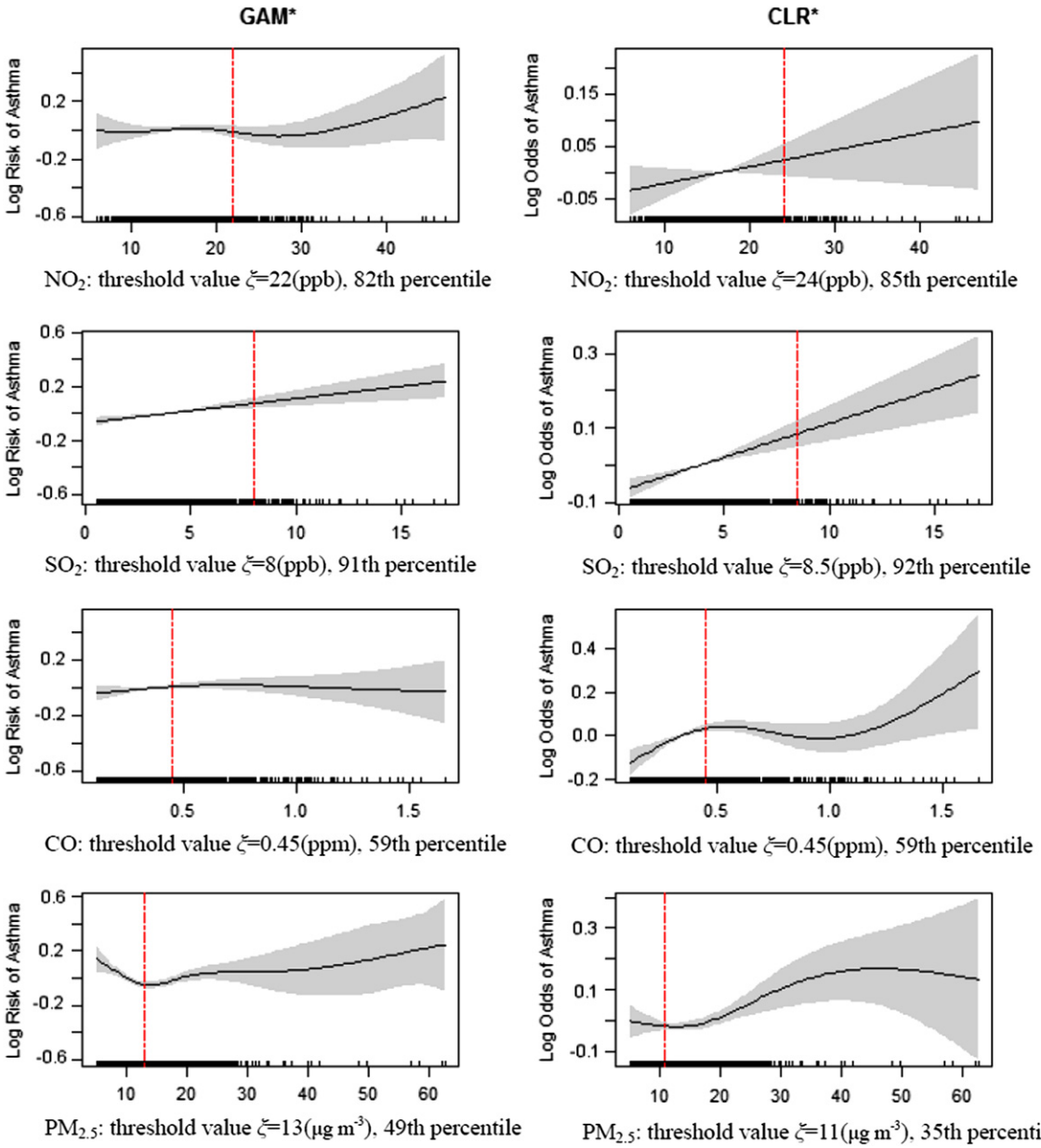

Fig. 3. Estimated spline terms of concentration with 95% confidence bands showing non-linear relationships between pollutant concentrations and daily asthma events, using 5-day moving average of pollutant concentrations. Vertical reference lines show estimated threshold parameters using profile likelihood method corresponding to each pollutant and model (*CLR: conditional logistic regression; GAM: generalized additive model.).

The seasonal effects of pollutants can be examined using an interaction term of concentration by season in the generalized additive model (2). Most associations are found for SO_2 and $PM_{2.5}$ in summer and spring respectively, often with much larger effect sizes than the reported overall effect that combines all seasons. (Appendix A.8 presents exposure effects by season under the interaction model.) Significant seasonal main effects with the following ordering of effect sizes were found in most models: fall > winter > spring > summer, thus, the fall peak of asthma counts is captured by the main effect of season, and cannot be attributed to the pollutants considered (little or no significant results were noted for exposure effects in fall across the multiple models). As pointed out in the literature previously, it may be more difficult to identify pollution-related events in the fall season due to the much larger number of visits resulting from other triggers, especially, those associated with the start of the September school year (Silverman et al., 2005; Johnston et al., 2005). We also fitted the model that adds an interaction term of concentration above the threshold by season in the generalized additive model (3). Instead of trying to estimate a season-specific threshold, which introduces three new parameters and additional non-linear terms in the model, the same thresholds as in Table 5 were used for this interaction analysis. Significance of the thresholds for $PM_{2.5}$ is found across seasons (Appendix A.9). Association of asthma and $PM_{2.5}$ concentration above the threshold are mostly found in spring, which has substantially larger effect sizes than other seasons or the overall effect combining all seasons. In the case-crossover analysis, adding interaction term by season was not possible as the exposure values are matched within season, and no contribution to the conditional likelihood can be measured since cases and controls have same value of season in most matched sets. Stratified analysis by season, performed as a sensitivity analysis, shows similar results as the interaction analysis. However, a stratified analysis by season faces the conceptual difficulty of

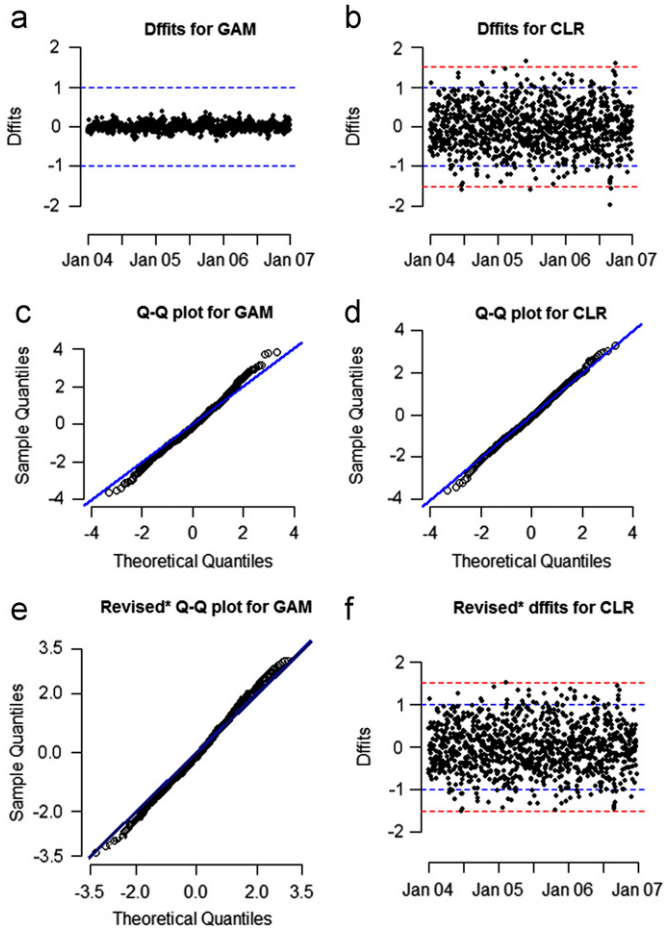

Fig. 4. Model diagnosis using DFFITS statistics and quantile–quantile plot (QQ-plots) for generalized additive model (GAM) and conditional logistic regression (CLR), using 5-day moving average of $PM_{2.5}$. Revised: deleted 11 days with $|\text{sample quantiles}| > 3.5$ in GAM and 6 days with $|\text{Dffits}| > 1.5$ in CLR.

estimating the spline terms corresponding to time and meteorological variables in a discontinuous manner for each season, and thus should be interpreted cautiously in this context.

Many of the studies just discussed support associations between lagged air pollutant exposures and acute asthma events, including emergency department visits, and the pollutants most closely associated with vehicle emissions, e.g., CO, NO_2 and fine fraction PM, have been suggested as those mostly strongly associated with asthma outcomes (Villeneuve et al., 2007; Schildcrout et al., 2006; Oyana and River, 2005). However, results of studies conducted in different cities and different countries can vary due to differences in geography, ethnicity, socioeconomic status, climate, pollutant mixtures, time activity patterns, study cohort including age group, heterogeneity between cites (especially in multicity studies) and other reasons.

A Canadian study has compared bi-directional case-crossover and time-series analyses, which were used to assess the associations between size-fractionated PM and asthma hospitalization among children 6–12 years old living in Toronto between 1981 and 1993 (Lin et al.; 2002). Both analyses revealed that coarse PM ($PM_{2.5-10}$) averaged over 5–6 days was significantly associated with asthma hospitalization. In a recent Japanese study, generalized additive model, generalized linear models and case-crossover analyses were compared to investigate effect of $PM_{2.5}$ on daily all-cause mortality (Ueda et al., 2009). Comparison of time-stratified case-crossover and time-series study, especially using asthma as outcome or a threshold concentration–response relationship, is relatively unexplored.

Although many different analytic approaches were used in these acute effect studies, none of them has considered the possibility of pollutant thresholds. In the Detroit Medicaid population, we found a 3–4% (no threshold) to 3–7% (with threshold) increase in emergency department asthma visits for a 9.2 $\mu g\,m^{-3}$ increase in $PM_{2.5}$. This effect size is larger than that found in Anchorage (Chimonas and Gessner, 2007) and Sydney (Jalaludin et al., 2008), but comparable to that found in Rio de Janeiro (Moura et al., 2009), Idaho (if we assume that $PM_{2.5}$ represents about half of PM_{10}) (Ulirsch et al., 2007), and the annual results in Edmonton. Much larger effects were seen when only the warmer season was considered (Villeneuve et al., 2007).

4.1. Significance of thresholds

Risk estimates based on an assumption of linearity may underestimate the true risk by diluting the effect across the whole spectrum of pollutant levels. Our findings for asthma associations with air pollutants, particularly for $PM_{2.5}$, showed consistent estimates of the threshold parameters in both time-series and case-crossover analyses. Fitting nonparametric smoothers on the exposure measure, though eminently feasible under the generalized additive model or conditional logistic regression framework, may not permit a direct interpretation of risk or odds ratios with literature values (or with standards and guidelines). Thus, the threshold model is appealing for natural interpretability.

Identification of concentration–response relationships is important for understanding toxicological mechanisms and susceptibility among populations. In particular, the concept and biological basis of a threshold for acute effects, in which a sufficient amount of a chemical must be present at its site of action to exert deleterious effects, is well-established and can be demonstrated for many toxic effects, although inter-individual variability in response and qualitative changes in the response pattern with concentration can make it difficult to establish a true "no effects" threshold (Eaton and Gilbert, 2008). In observational studies such as this one, it may be impossible to detect effects at low concentrations due to exposure misclassification, unmeasured or unknown covariates and confounders, and statistical power limitations. The present analysis showed that results of threshold models had increased effect sizes, consistency across model types, and enhanced statistical power compared to linear concentration–response models.

The presence of a threshold or a non-linear concentration–response relationship can have substantial implications in risk assessment and management, including standard setting (Holsapple and Wallace, 2008). The form of the US National Ambient Air Quality Standards, in which maximum concentrations at stated averaging times are specified for NO_2, CO, $PM_{2.5}$, O_3, SO_2 and Pb, represents a threshold-based approach. For example, the National Ambient Air Quality Standards for $PM_{2.5}$ is attained if ambient concentrations do not exceed 15 $\mu g\,m^{-3}$ on an annual average basis and 35 $\mu g\,m^{-3}$ on a 24-h basis (US EPA, 2009). We identified thresholds from 11 to 13 $\mu g\,m^{-3}$ for $PM_{2.5}$, quite close to the annual National Ambient Air Quality Standards level, which could be considered as providing support for this standard, although it seems more realistic to consider this as a coincidence, e.g., other guidelines suggest that risks of adverse outcomes (including asthma exacerbations) increase with $PM_{2.5}$ exposures with little evidence of a threshold below which no adverse health effects would be anticipated (WHO, 2005). The presence of thresholds also has implications for asthma education, air pollution warning systems, and disease management.

4.2. Limitations

The proposed method and our application in this Detroit Medicaid population have several limitations. There could be more than one change point in the model, leading to multiple threshold parameters where the profile likelihood based search may be infeasible. In this case, non-linear models could be used to find the maximum likelihood estimates and confidence intervals of the thresholds. However, the ease of implementation using the usual generalized additive model and conditional logistic regression models modules is an attractive feature of the profile likelihood method for practitioners when only one change point is present. Additionally, the threshold search procedure could be further refined by allowing different threshold parameters for each season or year.

Another issue in presenting results with multiple lags is the choice of the lag. We presented Akaike information criterion for each model in our results that could guide this choice. We also implemented a distributed lag non-linear model (Gasparrini et al., 2010) as a part of our sensitivity analysis, which revealed very consistent results for 3–5 day lags and moving averages (results presented in Appendices A.10 and A.11). In fact, the distributed lag models showed longer lag effects, e.g., $PM_{2.5}$ effects at 3–10 day lags and SO_2 effects at 3–13 day lags were found. We also acknowledge the possibility of residual confounding due to lagged effect of temperature. However, in limited sensitivity analyses, we did not notice such lagged effects for days with extreme temperatures.

Other inherent limitations in our analysis may potentially occur related to misclassification of the timing of events, the definition of the composite endpoint of asthma events being of low sensitivity or specificity, and ignoring that some claims may have come from the same child. Since hospitalizations may be more serious events than emergency department visits, our definition of asthma events leads to slightly inflated effect estimates when compared to using only emergency department visits without hospitalizations as the endpoint. However, all results remained significant for this more homogeneous and restricted sub-type of outcomes. We also assumed that claims made more than 30 days apart by the same individual are independent and ignored any residual subject-level correlation. Our inclusion criterion of continuous enrollment in Medicaid excluded children with more transient medical insurance coverage and more mobile residential histories (13% of the study subjects moved at least once in the 3 years). We also assumed that emergency department visits and hospitalization admissions for asthma were drawn from an essentially unchanging population, and that the use of an area-wide and daily average ambient air pollutant concentration provided a representative and unbiased exposure measure. While these are standard assumptions in such studies, ways to improve exposure estimates, in particular, have been investigated for this study (Li et al., 2011). Exposure measurement error in time-series air pollution studies was discussed by Zeger et al. (2000).

As for the $PM_{2.5}$ imputation, the error distribution could be estimated and used to generate multiple predictions, essentially by adding random error to the point prediction, and then used in outcome models multiple times to provide imputation uncertainty-adjusted parameter estimate (Little and Rubin, 2002). The multiple imputation strategy as a sensitivity analysis showed very similar results in terms of parameter estimate and inference for this data. Further exposure imputation issues have been discussed by Gryparis et al. (2009). Our analysis excluded O_3 due to a lack of data; it would be particularly interesting to examine this pollutant given that its effects have been considered to be a threshold function of concentration.

4.3. Conclusion

This study of the pediatric Medicaid population in Detroit indicates that SO_2 and $PM_{2.5}$ concentrations are associated with asthma emergency department visits and hospitalizations among children 2–18 years of age. Further, using both time-series and time-stratified case-crossover analyses, we demonstrate the existence of a threshold effect for $PM_{2.5}$ in the range from 11 to 13 $\mu g\, m^{-3}$. These findings were consistent across time-series and case-crossover models, and suggest that threshold models can provide enhanced statistical power compared to linear concentration–response models, and that effect estimates based on linear models (without thresholds) may underestimate the true risk.

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Appendix A. Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2011.06.002.

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